

WHAT IS CLAIMED IS:

1. A method of changing a functional surface binding specificity of a PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the  
5 steps of:
  - introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and
  - detecting a resultant change in the functional surface binding specificity of the PAS domain.
- 10 2. A method according to claim 1, wherein the binding specificity is a change in intermolecular binding affinity of the PAS domain.
- 15 3. A method according to claim 1, wherein the binding specificity is a change in intramolecular binding affinity of the PAS domain.
4. A method according to claim 1, wherein the binding specificity is manifested as a change in kinase activity or specificity.
- 20 5. A method according to claim 1, wherein the binding specificity is manifested as a change in channel patency or specificity.
6. A method according to claim 1, wherein the PAS domain is expressed by and within a host cell or animal.
- 25 7. A method according to claim 1, wherein the PAS domain is expressed by and within a host cell or animal, and the ligand is foreign to the host.
- 30 8. A method according to claim 1, wherein the PAS domain is expressed by and within a host cell or animal, and the change is detected indirectly as a change in host cell or animal physiology precorrelated with the change in binding specificity.

9. A method according to claim 4, wherein the PAS domain is expressed by and within a host cell or animal, and the change is detected indirectly as a change in host cell or animal physiology precorrelated with the change in binding specificity.
- 5       10. A method according to claim 5, wherein the PAS domain is expressed by and within a host cell or animal, and the change is detected indirectly as a change in host cell or animal physiology precorrelated with the change in binding specificity.
- 10      11. A method according to claim 1, wherein the PAS domain is selected from the group consisting of PAS kinase PAS A, NPAS2 PAS A, HIF2a PAS B, HIF1a PASB, ARNT PAS B and human ether-a-go-go related gene (HERG) N-terminal PAS.
- 15      12. A method according to claim 1, wherein the PAS domain is part of a larger protein selected from the group consisting of PAS kinase, NPAS2, HIF2a, ARNT, HIF1a and HERG protein.
- 20      13. A method according to claim 8, wherein the PAS domain is part of a larger protein selected from the group consisting of PAS kinase, NPAS2, HIF2a, ARNT, HIF1a and HERG protein.
14. A method according to claim 9, wherein the PAS domain is part of a larger protein selected from the group consisting of PAS kinase, NPAS2, HIF2a, ARNT, HIF1a and HERG protein.
- 25      15. A method according to claim 10, wherein the PAS domain is part of a larger protein selected from the group consisting of PAS kinase, NPAS2, HIF2a, ARNT, HIF1a and HERG protein.